REMARKS

Claims 16, 17, 21-25, 27 and 28 are pending. Claims 16 and 25 are amended. Claims 1-15, 18-20, 26 and 29-39 are canceled. No new matter has been added by way of these amendments nor is any further searching required of the Office. Support for the amendments is provided in the provisional application and throughout the specification as filed. Accordingly, entrance of these amendments and consideration of the remarks below is respectfully requested.

Withdrawn Rejections

Applicants gratefully acknowledge that the Office has decided the various rejections raised under 35 U.S.C. § 112, 1st and 2nd paragraphs, the anticipation rejections in view of Jensen, *et al.*, and the Wolozin patent, and the obviousness rejections in view of the Beire patent and the Hashimoto article.

Clarity

Claim 16 was objected to for reciting an abbreviation without explicitly defining it. Claim 16 has been amended to correct this situation.

Enablement

The Office has again rejected the pending claims because the claim set encompasses an assay where the NACP/α-synuclein is obtained from different sources.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)

The Office has failed to articulate a *prima facie* case regarding the alleged lack of enablement of the pending claims. The Office has alleged that comparing samples from the same source is "essential" for the operation of the claimed invention. While Applicants agree that it

would be "best scientific practice" to use a single source for testing in both the control and experiment tubes, it is not essential to do so. The use of best scientific practices is not a requirement for an applicant to obtain U.S. patent protection. All that is required is that the application teaches one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. Here, functionally equivalent samples of NACP/α-synuclein can be used in the claimed assay. Applicants readily contemplate a situation where recombinant NACP/α-synuclein obtained from one lot is used to test an inhibitor where the control lot is obtained from another source. So long as the two samples contain bona fide samples of NACP/α-synuclein, the assay will function. Accordingly, it is not "essential" that the same source of NACP/α-synuclein be used in the first and second samples. Thus, the present rejection should be withdrawn.

The Subject Matter Of The Pending Claims Is Novel

The pending claims were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Biere, *et al.* (U.S. Patent No. 6,184,351; herein after "the '351 patent").

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Here, the Office has alleged that the iron-catalyzed oxidative conditions recited in claim 16 is inherently met by the disclosure of the '351 patent, as evidenced by the teachings of Korge, *et al.*, and Bauminger, *et al.*, and additionally by the Lutz abstract. Specifically, the Office has alleged that the iron-catalyzed oxidative conditions recited in claim 16 inherently result because NACP/α-synuclein is exposed to oxidizing iron.

Applicants disagree with the position of the Office. Whether there are trace levels of oxidizing iron associated with each and every isolated NACP/α-synuclein sample is not the relevant

inquiry here. What the Office should be asking is whether there is enough oxidative iron present in each and every purified sample of isolated NACP/α-synuclein to achieve the claim limitation of an iron-catalyzed oxidative condition. Applicants submit that there is not. Applicants' position is supported by the experimental work in the '351 patent at col. 6, lines 28-39, which noted that "[d]uring the time frame of the experiment, no aggregates formed when incubated at room temperature or at 4°C." This disclosure proves that temperature rather than the presence of an iron-catalyzed oxidative state resulted in the aggregation of the protein discussed in this reference. That elevated temperature leads to NACP/α-synuclein aggregation is not a new finding, since this observation was first reported by Hashimoto, *et al.*, in 1998. See, Hashimoto, *et al.* (1998) *Brain Res.* 799(2):301-306.

Rather than rely upon this fact alone to establish the novelty of the claimed subject matter, Applicants have amended claim 16 to recite "adding an amount of exogenous ferric ion or exogenous ferrous ion and hydrogen peroxide effective to aggregate NACP/ α-synuclein." Support for this claim language is found, for example in Examples 1 and 2 of the present application. Here, the samples were incubated with 0, 1 10, or 100 μM ferric ion or 100 μM ferrous ion and H_2O_2.

The '351 patent does not teach the addition of exogenous iron ions to produce an iron-catalyzed oxidative condition. Because the '351 patent fails to teach all the limitations of the claimed invention, the reference does not anticipate the pending claims. Accordingly, this rejection should be withdrawn.

The Pending Claims are Non-Obvious

Claims 16-17, 24-25 and 27 were rejected under 35 U.S.C. § 103 as allegedly being obvious over Jensen, *et al.* (Biochem J. 323:539-546 (1997); hereinafter "the Jensen reference") as evidenced by Harris, *et al.* (Exp. Neurology 131(2) 193-202 (1995); hereinafter "the Harris reference") and further in view of Jenner, *et al.* (Ann. Neurology 44(S1):S72-S84(1998); hereinafter "the Jenner reference").

The examiner bears the burden of establishing a prima facie case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of

coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Third, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

Applicants submit that the Office has failed to articulate a prima facie case of obviousness. First, there is no motivation present in any of the references, whether taken alone or in combination with one another, that would lead one of ordinary skill in the art to combine or modify the cited references to achieve the claimed invention. This fault is primarily illustrated by the strained interpretation of the Harris reference and how it relates to the Jensen reference. The lack of the requisite motivation is also seen in the citation of the Jenner reference, which amounts to at best an invitation to experiment. Lastly, contrary to the characterization of the Office, the cited references do not teach all the limitation of the claimed invention. This is seen primarily in the discussion of the Jensen reference.

The Office begins its argument alleging that the Jensen reference teaches a method for identifying molecules that inhibit the aggregation of Aβ and synucleins. Office Action, page 6, section 14. Specifically, the Office pointed to page 540, col. 2, lines 24-44 of the Jensen reference to support the allegation that the method disclosed in the paper was directed to "inducing aggregation of amyloidogenic proteins." *Id.* Upon review of the Jensen reference, however, it is clear that this paper does not teach such a method.

The Jensen reference is concerned with proteins or peptides which effect Aβ aggregation and does not discuss α-synuclein aggregation at all. For example, the paper states that it sought to study the effects of regions of α-synuclein other than the NAC which might "promote Aβ aggregation." Jensen, *et al.*, page 539, col. 2, lines 8-22. This stated purpose of the paper is also seen in the

Experimental section, under the heading, "Effect of α– and β–synuclein on Aβ aggregation." *Id.* at 540, col. 2. In fact, the term "aggregation appears 11 times in the text of the article and each time the text speaks only of Aβ aggregation and is completely silent regarding the aggregation of α–synuclein. In view of these observations, one of ordinary skill in the art would not consider the Jensen reference as teaching a method for identifying molecules that inhibit α-synuclein aggregation. Accordingly, this paper fails to teach the method steps of the claimed invention.

Regarding the lack of motivation to combine or modify, the Office faced the problem of introducing an oxidizing condition into the method steps alleged taught in the Jenson reference. The Office cited the Harris reference for the proposition that "contact of A-beta with NACP taught by Jensen is equivalent to exposure to an oxidative condition which is noted to provide aggregation." Office Action, page 7. The Harris reference does indeed refer to oxidative injury and Alzheimer's disease. However, it is critical to note that this reference discusses Aβ generated free radicals which were hypothesized as promoting neurodegeneration. Harris, *et al.*, Abstract. The Harris reference said nothing about an oxidizing condition, let alone an iron-catalyzed oxidative condition that promoted NACP/α-synuclein aggregation. Beyond the Office's conclusory statement, there is no support whatsoever in either the Jensen or Harris references which would cause one of ordinary skill in the art to conclude that contact of Aβ with NACP is equivalent to exposure of NACP/α-synuclein to an oxidative condition. As such, the Harris reference, whether read alone or in combination with the other cited references does not provide the requisite motivation to combine or modify the cited references to achieve the claimed invention.

The Office admits that the Jensen reference "does not teach using ferric or ferrous iron as a means of oxidizing the polypeptides to induce aggregation." Office Action, page 7. The Office then looks to the Jenner reference to supply the missing iron-catalyzed oxidative conditions step of the claim to the Jensen reference. The Jensen reference does hypothesize a role via the Fenton reaction for an iron-catalyzed oxidative state which might contribute to the development of Parkinson's disease, but the teachings of the reference stop there. There is no suggestion, and not even a hint contained within the four corners of the Jensen reference that would suggest modifying the teachings of the other references to achieve the claimed invention. Certainly there is no portion of the Jensen reference that teaches or suggests adding exogenous iron to produce an iron-catalyzed

oxidative state. At best, the Jensen reference is an invitation to experiment in the direction that Applicants have to develop an assay for studying Alzheimer's disease. Such an invitation does not rise to the level of a suggestion to combine or modify the cited references to achieve the claimed invention.

In view of the deficiencies of the cited references discussed above, it is clear that the Office has failed to carry its burden to articulate a prima facie case of obviousness. As such, the present rejection should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 220002065000.

Respectfully submitted,

Dated: February 15, 2006 By: _____

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